REMARKS

Claims 15-19 are pending.

The rejection under 35 U.S.C. §112

Claims 15-19 were rejected for lack of enablement.

The Examiner argued that the data presented in the examples of the present application, derived from administering xenon to tissue culture cells representing an *in vitro* model of sepsis, could not be extrapolated to the actual treatment of sepsis because the art teaches that *in vivo* models of sepsis, rather than *in vitro* models, should be used. See the Office Action, page 5:

> The sourcebook of models for biomedical research directs one of ordinary skill in the art to the use of animal models in sepsis (pages 473 and 474 of: Sourcebook of Models for Biomedical Research Humana Press; P.Michael Conn Ed.; 2008 New Jersey).

The Applicants respectfully submit that the Examiner is incorrect in interpreting the publication referred to in the quote above (hereinafter "Conn") as "direct[ing] one of ordinary skill in the art to the use of animal models in sepsis" if such an interpretation includes the implicit assumption that *in vitro* models are not also useful.

Conn reviews some *in vivo* models of sepsis and discusses the benefits and drawbacks of those models. Conn does not mention *in vitro* models. There is no basis for concluding that this failure to discuss *in vitro* models of sepsis represents a teaching that *in vitro* models of sepsis are unreliable or are not to be used. It is certainly plausible that both types of models may be useful

and Conn simply chose to discuss one type rather than the other. Furthermore, nothing in Conn contradicts the well-known fact that *in vitro* models have their own benefits compared to *in vivo* models. For example, systemic changes in an animal (*e.g.* changes in blood pressure, body temperature *etc.*) during *in vivo* testing can obscure effects of a drug which might be revealed more clearly using an *in vitro* model.

In the following excerpts from the Office Action (page 6), the Examiner referred to two other publications as supporting his position that *in vitro* models of sepsis cannot be used to establish the enablement of the present claims:

> "Since *in vitro* cell culture models cannot account for "unknown" mechanisms of action, which are detected in live animals (where all the relevant interactions occur), the predictive value of non-animal alternative tests is limited at present." (page 482 of: Risk Assessment of Chemicals: An Introduction Second Edition; C.J. van Leeuwen and T.G. Vermeire Eds. 2007, Springer; Dordrecht, The Netherlands).
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> ...
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> Anderson et al. (page 743 of: Journal of Antimicrobial Chemotherapy 2008, 62, 738-745) comments on in vitro studies: ". ..given the exploratory nature of the study, all findings should be considered to be hypothesis generating. Further confirmatory research is needed to understand the mechanisms." And; ". . .and taken together, our findings provide scientific direction for future research in this area. ***Lastly, as in all in vitro research, we cannot predict how our findings translate into patients.*** The *in vivo* system is many times more complex than *in vitro* conditions. . . ". (Examiner added emphasis).

The Applicants respectfully submit that these publications cannot support this enablement rejection because both publications are directed to areas that have nothing to do with sepsis. The van Leeuwen publication deals with predicting chemical toxicity; the Anderson publication deals with the effects of cytokines and sex hormones on zidovudine- and lamovudine-triphosphate concentrations. Even if *in vitro* tests are unreliable in those areas, that would say nothing about

the reliability of *in vitro* tests in sepsis, given that those areas have very little, if any, connection to sepsis.

The Office Action, at page 6, also referred to another publication in support of this rejection:

> Frantz (Nature Reviews Drug Discovery; 2003,2, page 501) teaches that the use of cell culture and recombinant human cells provide valuable alternatives to animal experiments but these studies still cannot predict the integrated response of a potential drug as accurately as living systems in which a combination of genetic, biochemical, physiological, pathological and environmental influences work in concert (left column).

However, Frantz, although arguing that *in vivo* tests are important to the pharmaceutical industry, made it clear that *in vitro* tests are also valuable. See left column, third paragraph: "There have been major advances in the use of cell culture and recombinant human cells, and *in silico* approaches are also providing valuable alternative to animal experiments ..."

Even if, for the sake of argument, it is assumed that *in vivo* models of sepsis are generally regarded in the art as preferable to *in vivo* models of sepsis, that should not lead to a conclusion that the *in vitro* tests described in the present application do not provide enabling support for the present claims. The enablement requirement obligates the applicant to teach those skilled in the art how to practice the claimed invention without undue experimentation, but it imposes no particular means by which that obligation is satisfied. If the applicant chooses a means which does, in fact, teach those skilled in the art how to practice the claimed invention without undue experimentation, that should end the enablement inquiry. It cannot be then argued that the applicant's disclosure is defective because there might have been some other, perhaps better,

way the applicant might have chosen to enable the invention.[1] Enablement sets a bar that the applicant must clear, but there is no requirement that the bar be cleared by any particular distance.

In the Amendments filed January 6, 2009 and June 5, 2009, the Applicants explained that, due to the conserved nature of the molecular events underlying apoptosis in various cell types and the strength of the results in the examples of the present application, the *in vitro* tests disclosed in the examples of the present application provide an enabling disclosure for the reduction of apoptotic cell death in endothelial cells of the intestine during sepsis. Having thus enabled the claimed invention, the Applicants were under no obligation to provide additional, *in vivo* testing.

Furthermore, much of the argument provided in the Office Action to support this rejection appears to be concerned with questions of utility, i.e., whether the invention will work. For example, see page 8: "All Applicant has is a general idea based upon some *in vitro* data with only the intimation that *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture* can work." [underscoring and italics in original] See also page 7: "In other words, *in vitro* methods can be used to generate ideas and develop hypotheses but cannot be used alone for making broad sweeping assertions about how the *in vitro* results might work in a complex biological system ..."

[1] *See, e.g., The Telephone Cases*, 126 U.S. 1, 536, 8 S.Ct. 778, 31 L.Ed. 863 (1888) ("The law does not require that a discoverer or inventor ... must have succeeded in bringing his art to the highest degree of perfection; it is enough if he describes his method with sufficient clearness and precision to enable those skilled in the matter to understand what the process is, and if he points out some practicable way of putting it into operation.").

Case law makes clear that there is no requirement for an applicant to provide *in vivo* test results to establish utility. Rather, *in vitro* results can be sufficient. See, e.g., *In re '318 Patent Infringement Litigation*, 583 F. 3d 1317, 1324-1325, 92 U.S.P.Q. 2d 1385, 1389 (Fed. Cir. 2009): "We have held that results from animal tests or in vitro experiments may be sufficient to satisfy the utility requirement." [footnote omitted]. See also *In re Isaacs*, 347 F. 2d 887, 889, 146 U.S.P.Q. 193, 195 (C.C.P.A. 1963):

> [B]oth the examiner and the board felt that appellants should have submitted evidence of in vivo tests. No authority has been cited and we have been able to find none which requires that in order to secure a patent, utility of a pharmacologically active substance must be proved by in vivo testing.

In the same vein, as previously discussed, case law does not require *in vivo* test results to establish utility when couched as part of the enablement requirement (i.e., "how to use" the invention). Instead, in both the present application as well as *'318 Patent Infringement Litigation* and *Isaacs*, the fundamental question is whether an application which does not provide working examples to demonstrate that the invention works when carried out in precisely in the manner in which it is claimed nevertheless does provide a disclosure that can be extrapolated by those skilled in the art to the claimed invention.

In view of the lack of teaching in the art that *in vitro* models of sepsis are inadequate, the strong data showing inhibition of apoptosis in the examples of the present specification, and the clear teaching of the case law that such *in vitro* results may be sufficient for enablement, it is respectfully requested that this rejection be withdrawn.

Finley et al., 1975, Surgery 78:87-94 (Finley)

On page 9, the Office Action stated:

> Finley et al. (Surgery, 1975, 78(1), 87-94) teach methods of injecting ^{133}xenon dissolved in saline solution into patients with sepsis (page 87, right column and page 88, lower right column and Discussion page 92). Please note that this reference is not being applied against the instant claims based upon inherency because of the enablement problem above but may be applied in the future if the enablement rejection is overcome.

Finley used xenon (^{133}Xe) as a radioactive tracer in patients with sepsis as a means of measuring blood flow. There is no mention of the use of xenon to treat sepsis in Finley. Furthermore, since xenon was used as a radioactive tracer, it would almost certainly have been used in tiny quantities, as is common for the use of any substance as a radioactive tracer. Therefore, the dose of xenon used in Finley would have been several orders of magnitude below the dose that could cause any known physiological effects of xenon. Again, this is common for the use of substances as tracers; it is important that the tracer substance not have a physiological effect at the dose used, since such a physiological effect might obscure the biological phenomena that are being studied. Thus, the dose of xenon administered in Finley would have been very much lower than "an effective amount," as recited by the present claims.

The time for responding to the Office Action was set for June 24, 2010. Therefore, it is believed that this paper is timely. If this is in error, please treat this paper as containing a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit

the filing of this paper and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Director is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

Date: June 14, 2010

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